

Management of chronic pancreatitis

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Abstract. Chronic Pancreatitis (CP) is characterized by progressive inflammation, fibrosis, and scarring of the pancreas, leading to exocrine and endocrine insufficiency and increased risk of pancreatic cancer. A mechanistic definition introduced by an international consortium in 2016 and subsequent European guidelines have shaped diagnostic and management strategies. CP presents either symptomatically or asymptotically, with distinct histological features. Imaging modalities like CT and MRI play critical roles in diagnosis, supplemented by Endoscopic Ultrasound for early detection and nuanced assessments. Surgical interventions are reserved for complications and intractable pain, with a trend towards early surgery to prevent opioid dependency and neuropathic pain development. Multifactorial etiologies, including genetic and environmental factors, influence CP's progression. Management necessitates an interdisciplinary approach, integrating pain management, surgical options, and emerging artificial intelligence tools for better disease and complication stratification.

Keywords: chronic pancreatitis, management, complications

Introduction

Persistent inflammation, fibrosis, and scarring within the pancreas, characteristic of chronic pancreatitis (CP), lead to a gradual deterioration and eventual loss of pancreatic functions across its exocrine (acinar) and endocrine (islet cells) systems, as well as its ductal structures. Clinically, this condition is frequently linked with symptoms such as abdominal discomfort, deficiencies in both exocrine and endocrine functions, an increased risk of secondary pancreatic cancer, and various other complications¹.

Definition

For many years, the topic of CP remained a contentious issue without any established international guidelines. It wasn't until 2016 that a globally diverse group of specialists from the

United States, India, Europe, and Japan came together to introduce a novel, internationally recognized definition based on *mechanistic definition: CP is a pathologic fibro-inflammatory syndrome of the pancreas in individuals with genetic, environmental and/or other risk factors*². In 2017 the European Society of gastroenterology published the European recommendations

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including diagnostic treatment complications and prevention. The international Consensus guidelines for CP in collaboration with The International Association of Pancreatology, American Pancreatic Association, Japan Pancreas Society, Pancreas Fest Working Group and European Pancreatic Club decided to start publishing from 2018 recommendations for each step in the management of this disease.

CP involves recurrent pancreatic inflammatory injury with progressive destruction of endocrine and exocrine tissue, variable clinical features, the presence of constitutional, environmental and genetic risk factors. CP is defined as a fibro-inflammatory syndrome in an individual with genetic, environmental or other risk factors who develops an abnormal and prolonged response to pancreatic stress³. The incidence and the prevalence of the CP are not very clear. The prevalence of CP ranges from 13.5 to 163 cases per 100,000 persons in a large number of heterogeneous studies, and the incidence of CP ranges between 5 and 31.7 per 100,000 person-years⁴⁻¹¹. Xiao et al reported based on high-quality cohort studies an incidence of 9.62 cases per 100,000 person-years¹².

Classification

CP typically presents in one of two clinical variants: a symptomatic form accompanied by various complications, and a form where the patient remains asymptomatic. Histologically, the disease is defined by three fundamental characteristics: extensive fibrosis, diminished acinar cell structures leading to atrophy, and modifications in the pancreatic ducts, evidenced by their distortion and enlargement¹³.

Additionally, CP can be categorized into obstructive CP, characterized by the enlargement of both the main pancreatic duct and smaller ductal structures. Another form is calcifying pancreatitis, which is often linked to specific causal factors. These distinctions are crucial for accurate diagnosis and appropriate management of the disease¹⁴. And mixed type involving both dilatation of MPD and calcifications.

Imagistics

As the preferred initial cross-sectional imaging technique, computed tomography (CT) plays a pivotal role in the assessment of CP, providing the ability to detect intraductal calcifications even without contrast injection, especially in moderate to severe cases of PC. Beyond this, CT scans with contrast can identify characteristic PC lesions, such as inflammatory phenomena, intraductal or parenchymal calcifications, atrophy in patients with pain, vascular complications, pseudocysts, and potential pancreatic cancer, though their sensitivity is limited in early-stage PC. Magnetic resonance imaging (MRI), particularly cholangio-pancreato MRI, has now become the benchmark for identifying pancreatic ductal abnormalities and diagnosing PC. CT scans also play a crucial role in ruling out other potential diseases with symptoms similar to PC¹⁵.

The advantage of MRI primarily lies in the diagnosis of early stages of PC, precisely describing ductal abnormalities, as well as detecting stones, pseudocysts, and the degree of fibrosis in diffusion sequences. When suspecting PC, it is recommended to perform both CT and MRI, as they are complementary and help in eliminating differential diagnoses. The presence of calcifications alone is not specific, nor are ductal abnormalities¹⁵. Common differential diagnoses include intraductal papillary mucinous neoplasm (IPMN) of the secondary ducts, which can present with calcifications and abnormal ducts. European Study Group on Cystic Tumors of the Pancreas¹⁶.

In cases of uncertainty about ductal anatomy, especially in early-stage PC, an MRI with intravenous secretin injection (SS-MRCP) can provide a more detailed analysis. It can be prescribed when an initial MRI is normal but there is clinical suspicion of PC¹⁷. The role of secretin-enhanced MRI has also been evaluated for quantifying pancreatic exocrine function, but the limited studies published on this are inconclusive, and this indication has not been widely accepted¹⁵.

Endoscopic ultrasonography

In early stages of CP (PC), morphological signs may be subtle, making

pancreatic echo-endoscopy an examination of choice. The described abnormalities include parenchymal changes and ductal anomalies. International experts have reported that the number of criteria required for a PC diagnosis using Endoscopic Ultrasound (EUS) cannot be definitively established, but the presence of 5 or more criteria supports a diagnosis, while 2 or fewer criteria negate it¹⁸.

In 2009, Catalano MF et al. published the Rosemont classification¹⁹, which details echo-endoscopic criteria for PC, can be useful but still requires further validation through additional studies. This classification distinguishes major and minor CP criteria (Table 1).

Table 1. Rosemont criteria

Major criteria	Minor criteria
Hyperechoic foci with shadowing (A)	Dilatation of the main duct ≥ 3.5 mm
	Hyper-echogenic foci without shadowing
Intraductal stones (A)	An irregular Wirsung's duct
	Hyper-echogenic duct wall
	Dilatation of the secondary ducts ≥ 1 mm
Honeycomb-like lobularity (B)	Increased non-contiguous lobularity.
	Cysts
	Stranding

According to the Rosemont classification, the PC diagnosis is defined as certain, probable, or indeterminate based on these criteria (Table 2).

Table 2. EUS diagnosis of CP on the basis of consensus criteria

I. Consistent with CP	1 major A feature AND ≥ 3 minor features
	1 major A feature AND major B feature
	2 major A features
II. Suggestive of CP	1 major A feature AND < 3 minor features
	1 major B feature AND ≥ 3 minor features
	≥ 5 minor features (any)
III. Indeterminate for CP	3 to 4 minor features, no major features
	major B feature alone or with < 3 minor features
IV. Normal	≤ 2 minor features, no major features

Therefore, the role of EUS in the PC diagnosis is not crucial. EUS is not beneficial in advanced stages with major morphological anomalies, as it does not provide additional information primary utility of EUS is in screening for an underlying tumor associated with PC, allowing for a biopsy of the suspicious nodule.

Risk factors

CP is a multifactorial disease with various contributing factors that influence its development and progression. Sustained alcohol intake, particularly over a span of 6 to 12 years, along with habitual smoking, are substantial contributing elements. The likelihood of developing CP augments with increased tobacco consumption; the relative risk (RR) is 2.4 for smokers indulging in less than a pack daily, which intensifies to 3.3 for those consuming more than a pack²⁰. Excessive alcohol use and smoking stand as independent predictors for the onset of CP²¹.

Genetic predispositions also play a crucial role in the onset of CP, with several genes being implicated in its pathogenesis. These include PRSS1, which is associated with hereditary pancreatitis, CFTR, known for its role in cystic fibrosis-related CP, SPINK1, CTSC, TRPV6, CaSR, CPA1, and Cel-Hyb. These genetic factors may alter the normal functioning of the pancreas, leading to the disease²².

Obstructive elements are also key in the development of CP. Anomalies can lead to obstructive CP by hindering the outflow of pancreatic enzymes²³.

Autoimmune pancreatitis is recognized as a contributing factor to the development of CP, even without a history of acute pancreatitis attacks²⁴.

Lastly, metabolic disturbances have been linked to the onset of CP, where high levels of calcium or triglycerides in the blood contribute to pancreatic inflammation and damage.

Table 3. Risk factor for CP

Chronic Alcoholism	$> 6 - 12$ years	
Chronic Smoking	Relative Risk (RR)	2.4 < 1 /day,
		3.3 > 1 /day
Hereditary Factors	PRSS1, CFTR, SPINK1, CTSC, TRPV6, CaSR, CPA1, Cel-Hyb	
Obstructive Factors	Pancreas divisum, post-traumatic stenosis, slow-growing tumor, pancreatic malformations	
Immunological Factors	Autoimmune pancreatitis	
Metabolic Factors	Hypercalcemia	
	Hypertriglyceridemia	

Complications

A vast majority of individuals with CP will experience recurrent acute or chronic pain, necessitating comprehensive management. This pain often leads to opioid dependency, social withdrawal, and issues in family and work life. The underlying pathophysiology is intricate, involving various pathways, including changes in the function of the peripheral and/or central nervous system and induced sensitization phenomena. The neuropathic component is strongly inferred from the clinical presentation. Management should be interdisciplinary and conducted in specialized settings, considering psychological and social aspects. To alleviate pain, current guidelines suggest combining painkillers with behavioral therapy, adjuvant treatments targeting neuropathy (such as Gabapentin and Pregabalin), antidepressants with significant neuropathic efficacy (serotonin-noradrenaline reuptake inhibitors), and antioxidants. The prolonged prescription of opioids or their derivatives is strongly discouraged due to the risks of dependency, social isolation, paradoxically induced pains, and inefficacy in treating neuropathic pain²⁵.

Endoscopic and surgical treatments should be tailored to the individual in specialized settings. These two strategies are complementary and require interdisciplinary discussion for optimal management. For patients with signs of ductal obstruction, an endoscopic approach using a pancreatic stent may be employed, potentially in conjunction with extracorporeal shock wave lithotripsy for cases with single proximal intraductal macro-calcifications (Table 4)¹⁸.

Table 4. Indication for endoscopic treatment

Decompression of the main pancreatic duct
Management of a pancreatic fistula
Fragmentation of calcifications (>1 cm) through extracorporeal lithotripsy
Drainage of symptomatic pseudocysts.
Decompression of the biliary tract

Patients with early-stage disease presenting with proximal obstruction of the main pancreatic duct are ideal candidates for such interventions.

Exocrine pancreatic insufficiency (EPI) is another significant complication, leading to issues like steatorrhea and malnutrition. EPI can be quantitatively assessed through fecal elastase measurement, with levels below 200 µg/g of stool indicating insufficiency²⁶.

Type 3c diabetes, also known as pancreatogenic diabetes, arises specifically due to the pancreatic damage caused by chronic inflammation²⁷. The loss of glucagon production in Type 3c diabetes mellitus (T3cDM) increases the likelihood of severe hypoglycemic episodes because the body's natural glucagon response is impaired²⁸.

Pancreatic adenocarcinoma is a well-recognized risk associated with CP. cumulative risk of cancer is 2% after 5 years and 4% after 15 to 20 years. This risk is even more pronounced in those associated with PRSS1 mutations, with an incidence of 10, 19, and 53.5% at 50, 60, and 75 years, respectively²⁹. These complications highlight the need for a comprehensive management approach to CP, addressing both symptom control and the prevention of associated conditions.

The integration of artificial intelligence (AI) could potentially enhance the stratification of pancreatic cancer risk among individuals with CP³⁰. Additionally, AI offers promising utilities in distinguishing pancreatic cancer from pseudo tumoral manifestations of CP, potentially refining diagnostic accuracy³¹.

Surgical intervention in CP is primarily indicated for persistent pain that is unresponsive to other treatments and for the suspicion of a neoplastic process (with a recommendation level of 1A). It is also indicated for certain local complications, such as stenosis of the duodenum or common bile duct, gastrointestinal bleeding caused by rupture of pseudoaneurysms or erosion of major blood vessels, significant pseudocysts, and internal pancreatic fistulas³².

In the clinical management of CP, early surgical intervention is preferred over late surgical approaches. This paradigm shift is

primarily driven by clinical evidence indicating that extended durations of unmitigated pain and the consequent prolonged reliance on opioids are strongly associated with the development of opioid dependence. This phenomenon is further elucidated in the study by Bouwense SA et al., which revealed that patients with CP exhibit altered central processing of nociception when compared to individuals without the condition³³. The development of neuropathic pain, a direct outcome of such altered nociceptive processing, poses significant challenges in pain management, often rendering conventional therapeutic approaches ineffective³².

In the context of morphine-dependent CP, surgical guidelines stipulate distinct interventions based on the morphological state of the pancreas. When the cephalic diameter exceeds 40 mm and the MPD is greater than 5 mm, the recommended procedures are a duodenal preserving head resection, such as the Frey (Berne or Beger) techniques or a cephalic pancreatoduodenectomy. For those with morphine-dependent CP exhibiting a normal cephalic diameter but an MPD greater than 5 mm, a lateral pancreatojejunostomy, with the possibility of an extension, may be considered. In cases of groove pancreatitis where conservative treatment has not yielded results, a cephalic pancreatoduodenectomy is the suggested course of action^{3,32}.

For patients suffering from hereditary pancreatitis, the guidelines recommend a total pancreatectomy, with the option of islet transplantation, to preserve endocrine function and manage the disease effectively³⁴.

Conflict of interest

The authors have declared that no competing interests exist.

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